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AMENDMENT UNDER 37 C.F.R. §1.116		
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	First Named Inventor	NOLAN, GARRY P.
	Application Number	09/918,601
	Filing Date	July 30, 2001
	Group Art Unit	1627
	Examiner Name	WESSENDORF, TERESA D.
	Title	*"Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules"*

Sir:

This amendment is responsive to the Final Office Action dated July 25, 2003. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

1-22 (canceled)

23. (currently amended) A method ~~for *in vitro* screening for a cell whose phenotype is altered by expression of a transdominant intracellular bioactive peptide~~ of screening for a peptide that alters the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library comprising at least 10^4 different retroviral nucleic acid sequences, into a plurality of cells, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding:

i) a candidate bioactive peptide of from 4 to 100 amino acids in length~~, wherein said candidate bioactive peptide comprises~~ comprising a randomized portion biased to minimize stop codons, ~~and wherein~~

b) expressing said retroviral nucleic acid sequences ~~are expressed in said cells~~ in said plurality of cells to produce a plurality of randomized peptides;

~~b)~~ c) screening said plurality of cells to detect ~~a cell exhibiting an altered phenotype due to the expression of a transdominant bioactive peptide~~ a peptide that (i) alters the cell phenotype when expressed, and (ii) is transdominant and intracellular.

24. (currently amended) A method ~~for *in vitro* screening for a cell whose phenotype is altered by expression of a transdominant intracellular bioactive peptide~~ of screening for a peptide that alters the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library comprising at least 10^4 different retroviral nucleic acid sequences, into a plurality of cells, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding:

i) a candidate bioactive peptide of from 4 to 100 amino acids in length~~, wherein said candidate bioactive peptide comprises~~ comprising a randomized portion biased to interact with a class of molecules, ~~and wherein~~

b) expressing said retroviral nucleic acid sequences ~~are expressed in said cells~~ in said plurality of cells to produce a plurality of randomized peptides;

~~b)~~ c) screening said plurality of cells to detect ~~a cell exhibiting an altered phenotype due to the expression of a transdominant bioactive peptide~~ a peptide that (i) alters the cell phenotype when expressed, and (ii) is transdominant and intracellular.

25. (currently amended) A method according to claim 23 or 24 further comprising the step:

isolating ~~said~~ a cell ~~exhibiting an altered phenotype~~ having an altered phenotype as the result of expression of said transdominant bioactive peptide.

26. (currently amended) A method according to claim 25 further comprising the step:

identifying said nucleic acid encoding said candidate bioactive peptide in ~~said~~ cell or identifying said candidate bioactive peptide in said cell.

27 (canceled)

28. (currently amended) ~~The method according to claim 23~~ A method of screening for a peptide that alters the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library comprising at least 10^4 different retroviral nucleic acid sequences, into a plurality of cells, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding:

i) a candidate bioactive peptide of from 4 to 100 amino acids in length comprising a randomized portion biased to minimize stop codons, wherein said randomized portion comprises codons having the sequence NNK, wherein N is selected from the group consisting of A, T, C and G, and K is selected from the group consisting of T and G;

b) expressing said retroviral nucleic acid sequences in said plurality of cells to produce a plurality of randomized peptides;

c) screening said plurality of cells to detect a peptide that (i) alters the cell phenotype when expressed, and (ii) is transdominant and intracellular.

29. (currently amended) ~~The method according to claim 24~~ A method of screening for a peptide that alters the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library comprising at least 10^4 different retroviral nucleic acid sequences, into a plurality of cells, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding:

i) a candidate bioactive peptide of from 4 to 100 amino acids in length comprising a randomized portion biased to interact with a class of molecules, wherein said randomized portion biased to interact with a class of molecules comprises the sequence set forth in SEQ ID NO:47, XXXPPXPXX, wherein X is a randomized residue;

b) expressing said retroviral nucleic acid sequences in said plurality of cells to produce a plurality of randomized peptides;

c) screening said plurality of cells to detect a peptide that (i) alters the cell phenotype when expressed, and (ii) is transdominant and intracellular.

30. (currently amended) The method according to claim 23 or 24 wherein said ~~candidate bioactive peptide is fused to a~~ retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding i) a candidate bioactive peptide, further comprises:

a nucleic acid sequence encoding a presentation sequence ~~capable of presenting said~~ that presents said candidate bioactive peptide in a conformationally restricted form; wherein a first portion of said presentation structure is joined to the N-terminal end of said candidate bioactive peptide, and a second portion of said presentation structure is joined to the C-terminal end of said candidate bioactive peptide.

31. (canceled)

32. (previously presented) A method according to claim 23 or 24 wherein said cells are mammalian cells.

33. (canceled)

34. (previously presented) The method according to claim 23 or 24 wherein said library comprises at least 10^5 different retroviral nucleic acid sequences.

35. (previously presented) The method according to claim 23 or 24 wherein said library comprises at least 10^6 different retroviral nucleic acid sequences.

36. (previously presented) The method according to claim 23 or 24 wherein said library comprises at least 10^7 different retroviral nucleic acid sequences.

37. (previously presented) The method according to claim 23 or 24 wherein said library comprises at least 10^8 different retroviral nucleic acid sequences.

38-39 (canceled)

40. (currently amended) The method according to claim 23 or 24 wherein said ~~candidate bioactive peptide is fused to a~~ retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding i) a candidate bioactive peptide, further comprises:

a nucleic acid sequence encoding a rescue sequence that when expressed is fused to said candidate bioactive peptide.

41. (currently amended) The method according to claim 23 or 24 wherein said ~~candidate bioactive peptide is fused to a~~ retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding i) a candidate bioactive peptide, further comprises:

a nucleic acid sequence encoding a stability sequence that when expressed is fused to said candidate bioactive peptide.

42. (currently amended) The method according to claim 23 or 24 wherein said ~~candidate bioactive peptide is fused to a~~ retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding i) a candidate bioactive peptide, further comprises:

a nucleic acid sequence encoding a dimerization sequence that when expressed is fused to said candidate bioactive peptide.

43. (currently amended) The method according to claim 23 or 24 wherein said ~~candidate bioactive peptide is fused to a~~ retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding i) a candidate bioactive peptide, further comprises:

a nucleic acid sequence encoding a targeting sequence that when expressed is fused to said candidate bioactive peptide.

44. (previously presented) The method according to claim 43 wherein said targeting sequence is selected from the group consisting of:

a) a localizing signal sequence capable of constitutively localizing said candidate bioactive peptide to a predetermined subcellular locale;

b) a membrane-anchoring sequence capable of localizing said candidate bioactive peptide to a cellular membrane; and

c) a secretory signal sequence capable of effecting the secretion of said candidate bioactive peptide.

45. (previously presented) A method according to claim 44 wherein said targeting sequence is a nuclear localization signal (NLS).

46. (previously presented) A method according to claim 44 wherein said targeting sequence is a myristylation sequence.

47. (previously presented) A molecular library of retroviruses comprising at least 10^5 different retroviral nucleic acid sequences wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding a candidate bioactive peptide of from 4 to 100 amino acids in length, wherein said candidate bioactive peptide comprises a randomized portion biased to minimize stop codons.

48. (previously presented) The molecular library of retroviruses according to claim 47 comprising at least 10^6 different retroviral nucleic acid sequences.

49. (previously presented) The molecular library of retroviruses according to claim 47 comprising at least 10^7 different retroviral nucleic acid sequences.

50. (previously presented) The molecular library of retroviruses according to claim 47 comprising at least 10^8 different retroviral nucleic acid sequences.

51. (previously presented) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said molecular library comprising at least 10^5 different retroviral nucleic acid sequences, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding a candidate bioactive peptide of from 4 to 100 amino acids in length, wherein said candidate bioactive peptide comprises a randomized portion biased to minimize stop codons.

52. (previously presented) The cellular library according to claim 51 wherein said constructs are integrated into the genome of said mammalian cells.

53. (canceled)

54. (currently amended) The molecular library of retroviruses according to claim 47, wherein said retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding a candidate bioactive peptide, further comprises: ~~candidate bioactive peptide is fused to~~ a nucleic acid sequence encoding a targeting sequence that when expressed is fused to said candidate bioactive peptide.

55. (currently amended) The molecular library of retroviruses according to claim 47, wherein said retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding a

candidate bioactive peptide, further comprises: ~~candidate bioactive peptide is fused to~~ a nucleic acid sequence encoding a rescue sequence that when expressed is fused to said candidate bioactive peptide.

56. (currently amended) The molecular library of retroviruses according to claim 47, wherein said retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding a candidate bioactive peptide, further comprises: ~~candidate bioactive peptide is fused to~~ a nucleic acid sequence encoding a stability sequence that when expressed is fused to said candidate bioactive peptide.

57. (currently amended) The molecular library of retroviruses according to claim 47, wherein said retroviral nucleic acid sequences comprising an insertion of a nucleic acid sequence encoding a candidate bioactive peptide, further comprises: ~~candidate bioactive peptide is fused to~~ a nucleic acid sequence encoding a dimerization sequence that when expressed is fused to said candidate bioactive peptide.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 were pending. Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 were examined and were rejected. No claims were allowed.

Claims 23-26, 28, 29, 30, 40-43 and 54-57 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. No new matter is added by these amendments. Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Claims 23-24 have been amended in accordance with the Examiner's suggestions for clarifying the object of the screening method. Claims 28 and 29 have been rewritten in independent form, to recite all the limitations of the base claim from which they depended. Claim 30 has been revised to recite a configuration of a presentation structure. Claims 40-43 and 54-57 have been amended to clarify the configuration of the fusion partner to the candidate peptide.

Claims 47-52 and 54-57 have been rejected under 35 U.S.C. 101 as directed to non-statutory subject matter. The Office Action states that the commercial value of such libraries does not have any bearing as to the utility requirement of the statute. Applicants respectfully submit that the libraries set forth in Claims 47-52 and 54-57 meet the requirements of 35 U.S.C. 101 and 112 for utility.

The libraries of the invention provide a useful research tool for identifying molecular targets, *e.g.* in signaling pathways, and for providing amino acid sequences that interact with such targets. As described in the specification, and as demonstrated in the attached Declaration, libraries of a certain complexity will have screening value.

It is the assertion of Applicants that the collection of biomolecules in a library has a utility that is ***distinct*** from the utility of an individual peptide. An individual peptide cannot serve as a research tool for identifying targets, because it has a limited capacity for interaction. It is ***only*** when one has a collection of sufficient size and complexity that a group of individual peptides becomes a useful library.

The position of the Patent Office and the Courts supports Applicants assertion that libraries have a patentable utility. For example, as set forth in the MPEP 2107.01, it is stated that "Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a **clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)**." (emphasis added).

As set forth in the MPEP, the claimed subject matter must have a specific and substantial utility. A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. The presently claimed libraries have a specific

utility. The libraries are useful in specific screening methods, such as those taught by Applicants, and are useful to identify molecular targets and biomolecules in cells.

The presently claimed libraries provide an experimentally proven resource for screening. A Declaration from Dr. Masuda, previously submitted in co-pending application 09/727,715, is attached herewith. The Declaration provides an explanation and statement as to the usefulness of the presently claimed libraries.

Several features of the claimed invention are important for this utility. One aspect is the retroviral vector, which transports the nucleic acid sequence into the cell, and provides the transcriptional elements for expression. Another aspect is the sequence encoding the candidate bioactive peptide, which is randomized as described in the specification, and which falls into a particular size class. A third aspect is the presence of the fusion partner, which provides additional functionality.

One of the most important aspects of the claimed invention is the complexity, which is recited to be at least 10^4 different sequences. The complexity allows one to have confidence that the library will provide for an interaction of interest.

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. The presently claimed libraries have a substantial utility, because they provide a means of identifying specific compounds and targets.

Applicants acknowledge the Examiner's statement that "each case is treated on a case-to-case basis", and that the patentability of one library claim does not necessarily flow from the patentability of a different library claim. However, it is noted for the record that even in the last few weeks the Patent Office has issued claims reciting biochemical libraries of a scope and content similar to that of Applicants' claims. For example, a few recent patents include United States Patent 6,576,467, June 10, 2003; United States Patent 6,573,098, June 3, 2003; United States Patent 6,569,435, May 27, 2003; United States Patent 6,562,617, May 13, 2003; and United States Patent 6,562,576, May 13, 2003. Each of these patents specifically claims libraries, which claims have presumably have met the burden for patentability under 35 U.S.C. 101.

The Federal Circuit has recently emphasized the importance to biotechnology of patenting research tools. In *Integra Lifesciences I, Ltd. v. Merck KGaA* (Fed. Cir.) 02-1052, 02-1065, it was stated that "patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs." Even Judge Newman's dissent in this case maintained the importance of patenting research tools, stating that "A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an

assay kit, a laser device (as in Madey v. Duke University), or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or method, whether it is used to conduct research or for any other purpose."

Judge Newman also made an important point regarding the distinction between a compound for research, and a research tool. A research tool, such as the presently claimed libraries, provides a means for important biological testing; and is distinct from a compound having certain specific properties that can be the subject of research.

Applicants respectfully submit that the presently claimed libraries meet the requirements of 35 U.S.C. 101, in that they possess a specific and substantial utility.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 have been rejected under 35 U.S.C. 112, first paragraph.

The Office Action states that the specification does not teach a method by which a cell can be an in vitro screen using the recited step, but rather teaches an *in vitro* screening of bioactive molecules. The presently pending claims have been amended, and recite a method of screening for a peptide that alters the phenotype of a cell. Withdrawal of the rejection is requested.

The Office Action states that claims 23-38 are rejected under 35 U.S.C. 112, first paragraph because the specification does not reasonably provide enablement for the broadly claimed variables.

Applicants respectfully submit that one of skill in the art could practice the randomization of a peptide insert based on the teachings of the specification. The present invention provides methods and compositions to create, effectively introduce into cells and screen compounds that affect a signaling pathway. Little or no knowledge of the pathway is required, other than a presumed signaling event and an observable physiologic change in the target cell. The invention also provides for the isolation of the constituents of the pathway, the tools to characterize the pathway, and lead compounds for pharmaceutical development. By delivering the random sequences to cells and screening the same cells, without the need to collect or synthesize *in vitro* the candidate agents, highly efficient screening is accomplished. In addition, the present methods allow screening in the absence of significant prior characterization of the cellular defect *per se*.

As set forth on page 19, line 30 to page 20, line 9 of the application, "The candidate bioactive agents and candidate nucleic acids are randomized, either fully randomized or they are biased in their randomization, e.g. in nucleotide/residue frequency generally or per position. By "randomized" or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. As is more fully described below, the candidate nucleic acids, which give rise to the candidate expression products, are chemically synthesized, and

thus may incorporate any nucleotide at any position. Thus, when the candidate nucleic acids are expressed to form peptides, any amino acid residue may be incorporated at any position. The synthetic process can be designed to generate randomized nucleic acids, to allow the formation of all or most of the possible combinations over the length of the nucleic acid, thus forming a library of randomized candidate nucleic acids."

The specification further provides guidance (page 21, lines 11-19) that "in one embodiment, the library is fully randomized, with no sequence preferences or constants at any position. In a preferred embodiment, the library is biased. That is, some positions within the sequence are either held constant, or are selected from a limited number of possibilities. For example, in a preferred embodiment, the nucleotides or amino acid residues are randomized within a defined class, for example, of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc."

One of skill in the art could readily synthesize randomized molecular libraries encoding peptides of from 4 to 100 amino acids in length, using methods known in the art. Such methods are demonstrated in the Examples; see page 56, line 24 to page 57, line 7; and page 61, lines 5-23.

The specification provides substantial detail and guidelines for the composition of fusion partners for the randomized sequence. Where the fusion partner is a presentation structure, such structures are stated to include minibody structures, loops on beta-sheet turns and coiled-coil stem structures in which residues not critical to structure are randomized, zinc-finger domains, cysteine-linked (disulfide) structures, transglutaminase linked structures, cyclic peptides, B-loop structures, helical barrels or bundles, and leucine zipper motifs (page 7, lines 14-16).

As set forth in Figure 3, presentation structures comprising a coiled coil domain have been used in the methods of the invention to isolate peptides capable of high affinity interaction with the appropriate target. In general, coiled-coil structures allow for between 6 to 20 randomized positions. Specific sequences of coiled coil domains are provided in the specification at page 7, lines 25-32.

Another presentation structure, the "minibody", is essentially composed of a minimal antibody complementarity region. The minibody presentation structure generally provides two randomizing regions that in the folded protein are presented along a single face of the tertiary structure. This minimal domain is stable in solution and has been used in phage selection systems in combinatorial libraries (page 8, lines 5-13). Specific minibody presentation sequences useful in the methods of the invention are provided, *e.g.* SEQ ID NO:6.

The specification further provides substantial guidance in the selection of a targeting sequence. Suitable targeting sequences are stated to include binding sequences capable of causing binding of the

expression product to a predetermined molecule or class of molecules; sequences signaling selective degradation; and signal sequences capable of constitutively localizing the candidate expression products to a predetermined cellular locale, including a) subcellular locations such as the Golgi, endoplasmic reticulum, nucleus, nucleoli, nuclear membrane, mitochondria, chloroplast, secretory vesicles, lysosome, and cellular membrane; and b) extracellular locations via a secretory signal (page 9, lines 15-24).

Among these targeting sequences, Applicants note that Claim 45 specifically recites nuclear localization signals, which are short, positively charged (basic) domains that serve to direct the entire protein in which they occur to the cell's nucleus. Numerous NLS amino acid sequences are specifically recited in the specification, including those set forth in SEQ ID NO:7, 8, 9, 10, and 11. It is known in the art that NLSs incorporated in synthetic peptides or grafted onto reporter proteins not normally targeted to the cell nucleus cause these peptides and reporter proteins to be concentrated in the nucleus (page 10, lines 1-10).

Other specifically recited targeting sequences include membrane-anchoring sequences, for example those derived from CD8, ICAM-2, IL-8R, CD4 and LFA-1. Again, specific sequences useful in the methods are recited, for example specific residues of the IL-2 receptor beta-chain; of the insulin receptor beta chain; of neutral endopeptidase; human cytochrome P450 NF25; and the specific residues of SEQ ID NO:12, 13, 14, 15, and 16.

Specific amino acid sequences useful as myristylation sequences are also recited in the specification. This is a simple and effective method of membrane localization, which can be effected by the use of the amino acid residues in SEQ ID NO:17, 18, 19 or 20.

In conclusion, Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112, first paragraph. The law does not require that every detail of the working examples be reiterated as a limitation in the claims. It is not required that the applicant provide a working exemplification for every embodiment of a claim, nor to spell out every detail. See MPEP 608.01(h) "A patent specification is not intended nor required to be a production specification".

The present specification provides innumerable examples and specific sequences that can be used in the methods of the invention, to assemble the retrovirus comprising a randomized sequence and a fusion partner as set forth in the claims. One of skill in the art could readily use any one of the many specific amino acids sequence; and the guidelines for generating a randomized sequence, to generate a library for use in the methods of the invention. Withdrawal of the rejection is requested.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 have been rejected under 35 U.S.C. 112, second paragraph as vague and indefinite. The Office Action states that the claims fail to point out

what is excluded or included by the claim language. Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112, second paragraph.

The Examiner has objected to the use of the term "minimize" in the claims. Applicants respectfully submit that the term "minimize" apprises one of skill in the art of the metes and bounds of the invention. Applicants further draw the Examiner's attention to Claim 28, which has been rewritten in independent form, and recites the specific NNK codon usage, in accordance with the Examiner's suggestions.

The Office Action states that the metes and bounds of the terms "phenotype", "cell", "transdominant intracellular bioactive agent", "molecular library of biased randomized nucleic acids", and "classes of molecules", are unclear. Applicants respectfully submit that the meaning of these terms is clear to one of skill in the art, in view of the teachings of the specification, and as set forth in Applicants previous response.

The Office Action states that "the long list provided by Applicant appears not to be limited thereto but still include others not given in the list. It is apparent that the claim has not been circumscribed with particularity." Applicants respectfully submit that the terms phenotype, or cell, or class of molecules are understood by those of skill in the art, and are supported by the disclosure of the specification. It is not required that Applicants set forth in the claim every possible change in cellular phenotype. One of skill in the art can readily understand the use of a generic term – "phenotype" when it is supported by the description of a large number of species (for example: change in cell viability, change in RNA expression, alteration in cellular membrane potential, *etc.*), which fall within the genus.

The Office Action states that it is not clear as to the purpose of only screening cells without isolating and identifying the cells, and that in order that a cell be determined for phenotypic changes, isolation is required.

Applicants respectfully submit that one need not undertake an isolation step in order to identify a cell having an altered phenotype. There are many methods available for identifying a sequence of interest, without isolating a specific cell population. For example, one could transfect a population of cells with a randomized peptide; select for cells that grow in selective medium; and use PCR to amplify and identify the sequences conferring growth.

Claim 30 has been amended to delete the term "capable", which is stated by the Office Action as connoting uncertainty.

The Office Action states that claims 40-46 broaden the base claim. Applicants respectfully submit that claims 40-46 are proper dependent claims. Applicants respectfully submit that Claims 40-46 are properly written, and meet the requirements of 35 U.S.C. 112, second paragraph.

As set forth in the MPEP, "a dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope." In other words, a proper dependent claim shall not conceivably be infringed by anything that would not also infringe the basic claim.

The Office Action states that the base claim does not recite a conjugate for the nucleic acid or encoded bioactive agent. Applicants respectfully submit that the base claims recite the presence of sequences encoding a candidate bioactive peptide. Dependent claims 40-44 recite a nucleic acid further comprising a sequence encoding a specific additional sequence which when expressed is fused to the candidate bioactive peptide.

Whether the scope of the claim is altered by the fusion partner is not relevant to the test for a proper dependent claim, as recited in the MPEP. The proper test is whether any conceivable practice of the screening method set forth in Claims 40-46 would infringe the base claim. The answer to that question is clearly yes, because the method set forth in Claims 40-46 include every limitation of the method set forth in base claims 23 or 24.

The Office Action has rejected the claims amended in Applicants' previous response as follows.

1. The term "*in vitro* screening" is stated to be unclear. Claims 23 and 24 have been amended to clarify the preamble, and the term "*in vitro*" has been deleted.

2. The identifying step in Claim 26 is stated to be unclear in broadening the base claim. Applicants respectfully submit that, as discussed above and stated in the MPEP, a dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends.

3. The Office Action states that "the metes and bounds of the class of molecules recited in Claim 29 are not clearly circumscribed by Claim 29." Applicants respectfully request clarification of the Examiner's position. It is respectfully submitted that Claim 29 sets forth a specific structure, wherein a portion of the randomized peptide comprises the motif sequence set forth in SEQ ID NO:47. Therefore,

the metes and bounds are as stated – a peptide comprising a particular sequence motif. One of skill in the art would readily understand the meaning of this limitation.

In view of the above amendments and remarks, withdrawal of the rejections under 35 U.S.C. 112, second paragraph is requested.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 have been rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over Claims 1-12 of U.S. Patent no. 6,365,344.

Applicants respectfully submit that the present claims are not obvious in view of the claims of the '344 patent. The claims of the '344 patent require that the peptides (a) comprise a secretion signal sequence which is not native to a first plurality of mammalian cells (which cells express the peptide) and (b) act on a second cell second plurality of mammalian cells to generate a changed physiology in response to a transdominant bioactive peptide expressed by the first plurality of mammalian cells.

The present claims are unobvious in view of the claims of the '344 patent in that the method screens for peptides that act on the cells in which they are expressed; and because the claims recite specific sequence variations not taught in the claims of the '344 patent.

The Office Action states that "each of the copending applications and issued patents discloses said random library with biased stop codons"; and that "there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending applications".

Applicants respectfully submit that the text of the specification in the issued patent or copending application is not a factor in determining obviousness type double patenting. The only disclosure that is considered in the determination is the actual language of the claims. As set forth in *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967), the patent principally underlying the double patenting rejection **is not considered prior art**.

The analysis for double patenting considers only whether a claim is obvious in view of the teaching of another claim. While the analysis parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination, (see *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)), one considers only whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent. The disclosure of the patent may not be used as prior art.

One of skill in the art, upon reading the claims of the above-cited applications and patents, would not reasonable expect to be able to produce or use a library comprising a randomized sequence biased to minimize stop codons; and a randomized sequence biased to interact with a class of

molecules. Such features are not an obvious variation of the cited **claims**. There is no suggestion of such a library in the claims.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 have been provisionally rejected as being unpatentable over claims 23-38 of co-pending patent applications 09/727,715; 09/916,940; 08/963,368; or 08/787,738. Applicants respectfully submit that, for the reasons discussed above, the **claims** of the co-pending application would not suggest to one of skill in the art the use of a library having minimized stop codons or bias to interact with a class of molecules.

In view of the above remarks, withdrawal of the rejection is requested.

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If the Examiner finds that a Telephone Conference would expedite prosecution of this application, she is invited to contact the undersigned (650) 327-3400.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number RIGL-004CON3, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
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